Novelty Assessment Report

Paper: SYNC: Measuring and Advancing Synthesizability in Structure-Based Drug Design
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Abstract

Designing 3D ligands that bind to a given protein pocket with high affinity is a fundamental task in Structure-Based Drug Design (SBDD). However, the lack of synthesizability of 3D ligands has been hindering progress toward experimental validation; moreover, computationally evaluating synthesizability is a non-trivial task. In this paper, we first benchmark eight classical synthesizability metrics across 11 SBDD methods. The comparison reveals significant inconsistencies between these metrics, making them impractical and inaccurate criteria for guiding SBDD methods toward synthesizable drug design. Therefore, we propose a simple yet effective SE(3)-invariant \textit{\underline{SYN}thesizability \underline{C}lassifier} (SYNC) to enable better synthesizability estimation in SBDD, which demonstrates superior generalizability and speed compared to existing metrics on five curated datasets. Finally, with SYNC as a plug-and-play module, we establish a synthesizability classifier-driven SBDD paradigm through guided diffusion and Direct Preference Optimization, where highly synthesizable molecules are directly generated without compromising binding affinity. Extensive experiments also demonstrate the effectiveness of SYNC and the advantage of our paradigm in synthesizable SBDD. Code is available at \url{https://anonymous.4open.science/r/SYNC-C94D/}.

Core Task Landscape

This paper addresses: **Synthesizability Evaluation in Structure-Based Drug Design**

A total of **50 papers** were analyzed and organized into a taxonomy with **12 categories**.

Taxonomy Overview

The research landscape has been organized into the following main categories:

- **Synthesizability Scoring and Prediction Methods**
- **Generative Design with Synthesizability Constraints**
- **Retrosynthesis-Guided Molecular Design**
- **Computational Frameworks and Workflows for Synthesizable Design**
- **Application-Specific Structure-Based Design with Synthesis Considerations**
- **Enzyme Engineering and Biocatalysis for Synthesis**
- **Benchmarking and Evaluation of Synthesizability in Molecular Design**
- **DNA-Encoded Libraries and Polymer Design**

Complete Taxonomy Tree

- Synthesizability Evaluation in Structure-Based Drug Design Survey Taxonomy
- Synthesizability Scoring and Prediction Methods
  - Classical and Heuristic Scoring Approaches (2 papers)
  - [14] Synthetic accessibility scoring and its application to the high-throughput design of energetic molecules (Yining Zhang, 2025) View paper
  - [42] Assessing synthetic accessibility of chemical compounds using machine learning methods (Yevgeniy Podolyan, 2010) View paper
  - Machine Learning-Based Synthesizability Scoring (3 papers)
  - [21] MolPrice: assessing synthetic accessibility of molecules based on market value (Friedrich Hastedt, 2025) View paper
  - [25] FSscore: A Machine Learning-based Synthetic Feasibility Score Leveraging Human Expertise (Neeser, 2023) View paper
  - [27] FSscore: A Personalized Machine Learningâ□□Based Synthetic Feasibility Score (Rebecca M. Neeser, 2024) View paper
  - Retrosynthesis-Based Synthesizability Evaluation (2 papers)
  - [2] Integrating synthetic accessibility with AI-based generative drug design (Maud Parrot, 2023) View paper
  - [17] Evaluating Molecule Synthesizability via Retrosynthetic Planning and Reaction Prediction (Liu Song-tao, 2024) View paper
- Generative Design with Synthesizability Constraints
  - Structure-Based Generative Models with Synthesizability Optimization ★ (6 papers)
  - [0] SYNC: Measuring and Advancing Synthesizability in Structure-Based Drug Design (Anon et al., 2026) View paper
  - [4] Prompt-based 3d molecular diffusion models for structure-based drug design (L Yang, 2023) View paper
  - [9] MedSAGE: Bridging Generative AI and Medicinal Chemistry for Structure-Based Design of Small Molecule Drugs (Alexander S. Powers, 2025) View paper
  - [15] Synthesis-driven design of 3D molecules for structure-based drug discovery using geometric transformers (Li Yibo, 2022) View paper
  - [26] Enhancing Ligand Validity and Affinity in Structure-Based Drug Design with Multi-Reward Optimization (S Lee, 2025) View paper
  - [28] FragGen: towards 3D geometry reliable fragment-based molecular generation (Odin Zhang, 2024) View paper
  - General Molecular Generation with Synthesizability Integration (6 papers)

- [3] The elephant in the lab: synthesizability in generative small-molecule design (Sven Michael Papidocha, 2026) View paper
- [7] BPS2025-Automated structure-based drug design with generative deep learning (Jesse Weller, 2025) View paper
- [10] A flexible data-free framework for structure-based de novo drug design with reinforcement learning (Hongyan Du, 2023) View paper
- [31] Quantum-inspired Reinforcement Learning for Synthesizable Drug Design (Chen, 2024) View paper
- [46] ChemistGA: a chemical synthesizable accessible molecular generation algorithm for real-world drug discovery (Jike Wang, 2022) View paper
- [47] Open Macromolecular Genome: Generative Design of Synthetically Accessible Polymers (Seonghwan Kim, 2023) View paper
- Fragment-Based and Linker Design with Synthesizability (5 papers)
- [16] Structure-guided fragment linking algorithm enables chemically feasible ligand design with predicted binding modes (Marcin CieÅ□lak, 2025) View paper
- [20] Linker-GPT: design of Antibody-drug conjugates linkers with molecular generators and reinforcement learning (An Su, 2025) View paper
- [36] CReM-dock: de novo design of synthetically feasible compounds guided by molecular docking (Guzel Minibaeva, 2024) View paper
- [37] Retrosynthetic Analysis-Aware Fragment Linking for Structure-Guided Ligand Extension (A Katsuyama, 2025) View paper
- [38] Protein Structure-Based Organic Chemistry-Driven Ligand Design from Ultralarge Chemical Spaces (FranÃ§ois Sindt, 2024) View paper

- Retrosynthesis-Guided Molecular Design (6 papers)
- [5] Generate what you can make: achieving in-house synthesizability with readily available resources in de novo drug design (Alan Kai Hassen, 2025) View paper
- [11] SynTwins: a retrosynthesis-guided framework for synthesizable molecular analog generation. (Chen Shuan, 2025) View paper
- [18] Amortized tree generation for bottom-up synthesis planning and synthesizable molecular design (Gao, 2021) View paper
- [19] Synthesizable by Design: A Retrosynthesis-Guided Framework for Molecular Analog Generation (Chen Shuan, 2025) View paper
- [39] Fake it until you make it? Generative de novo design and virtual screening of synthesizable molecules (Megan Stanley, 2023) View paper
- [44] An algorithmic framework for synthetic cost-aware decision making in molecular design (Jenna C. Fromer, 2024) View paper

- Computational Frameworks and Workflows for Synthesizable Design (3 papers)
- [1] Recent advances in automated structure-based de novo drug design (Yidan Tang, 2024) View paper
- [8] Tackling the issue of confined chemical space with AI-based de novo drug design and molecular optimization (A. Talevi, 2025) View paper
- [49] MegaSyn: integrating generative molecular design, automated analog designer, and synthetic viability prediction (Fabio Urbina, 2022) View paper

- Application-Specific Structure-Based Design with Synthesis Considerations (12 papers)
- [6] Protein modeling and structure-based drug design (Gerhard Klebe, 2025) View paper
- [12] Regulating the N-oxidation selectivity of P450BM3 monooxygenases for N-heterocycles through computer-assisted structure-guided design (Liu Yang, 2025) View paper
- [13] â□¦ , Synthesis and Anti-Inflammatory Evaluation of 3-Substituted 5-Amidobenzoate Derivatives as Novel P2Y14 Receptor Antagonists via Structure-Guided Molecular â□¦ (S Mao, 2025) View paper
- [22] Medicinal chemistry projects requiring imaginative structure-based drug design methods (Nicolas Moitessier, 2016) View paper
- [24] Discovery of new 2,4-diaminopyrimidines derivatives as EGFRT790M kinase inhibitors: a structure-based approach with DFT calculation, drug-likeness, ADME-toxicity properties evaluation and MD simulation (M. T. Ibrahim, 2024) View paper
- [29] In-silico activity prediction, structure-based drug design, molecular docking and pharmacokinetic studies of selected quinazoline derivatives for their antiproliferative activity against triple negative breast cancer (MDA-MB231) cell line (Sagiru Hamza Abdullahi, 2022) View paper
- [30] LigBuilder: a multi-purpose program for structure-based drug design (Renxiao Wang, 2000) View paper
- [32] Structure-guided design and photochemical synthesis of new carbamo (dithioperoxo) thioates with improved potencies to SARS-CoV-2 3CLpro (Jie Xin, 2024) View paper
- [34] Structure-Guided Design, Synthesis, and Antivirulence Assessment of Covalent Staphylococcus aureus Sortase A Inhibitors (BindingDB, 2024) View paper
- [35] Design and chemical synthesis of integrin ligands (Dominik Heckmann, 2007) View paper
- [40] Design, Synthesis, Herbicidal Activity, and Structureâ□□Activity Relationship Study of Novel 6-(5-Aryl-Substituted-1-Pyrazolyl)-2-Picolinic Acid as Potential Herbicides (Tong Feng, 2023) View paper
- [50] Structure-Based Drug Design and Synthesis of Pyrrolidine-2,5-diones as Novel TNF-Î± Inhibitors (Yueying Yang, 2023) View paper

- Enzyme Engineering and Biocatalysis for Synthesis (3 papers)
- [23] DORA-XGB: An improved enzymatic reaction feasibility classifier trained using a novel synthetic data approach (Yash Chainani, 2024) View paper
- [33] Machine learning guided rational design of a non-heme iron-based lysine dioxygenase improves its total turnover number (R. Hunter Wilson, 2024) View paper
- [41] Mechanism-Guided Computational Design Drives meso-Diaminopimelate Dehydrogenase to Efficient Synthesis of Aromatic d-amino Acids. (Tianfu Wu, 2024) View paper

- Benchmarking and Evaluation of Synthesizability in Molecular Design (1 papers)
- [45] Breaking Bad Molecules: Are MLLMs Ready for Structure-Level Molecular Detoxification? (Lin Fei, 2025) View paper

- DNA-Encoded Libraries and Polymer Design (2 papers)
- [43] Design, synthesis and selection of DNA-encoded small-molecule libraries (BindingDB, 2009) View paper
- [48] Constructing epoxy polymer with significantly increased dielectric strength through molecular design by introducing deep trap (Yang Feng, 2025) View paper

Narrative

Core task: synthesizability evaluation in structure-based drug design. The field has evolved to address a central challenge in computational drug discovery—ensuring that computationally generated molecules can actually be made in the laboratory. The taxonomy reveals several complementary branches: some focus on scoring and prediction methods that estimate how easily a molecule can be synthesized (often using machine learning or rule-based heuristics), while others embed synthesizability constraints directly into

generative design workflows. A third major direction leverages retrosynthesis planning to guide molecular design, ensuring that proposed structures have plausible synthetic routes. Additional branches cover computational frameworks that integrate these considerations into end-to-end pipelines, application-specific design efforts (for example targeting particular proteins or disease areas), enzyme engineering for biocatalytic synthesis, benchmarking studies that evaluate synthesizability metrics, and specialized topics such as DNA-encoded libraries. Together, these branches reflect a shift from purely affinity-driven design toward practical, synthesis-aware strategies.

Recent work highlights contrasting philosophies: some methods prioritize rapid scoring to filter large virtual libraries (Synthetic Accessibility Scoring[14], FSscore[25]), while others tightly couple generative models with retrosynthetic feasibility checks (Amortized Tree Generation[18], Generate What You Make[5]). The original paper, SYNC[0], sits within the generative design branch that optimizes synthesizability during structure-based generation. It shares common ground with approaches like Synthesis-Driven 3D Design[15] and Multi-Reward Optimization[26], which balance binding affinity and synthetic accessibility in a unified objective. Compared to purely scoring-based methods, SYNC[0] and its neighbors aim to steer the generative process itself rather than post-hoc filtering, reflecting an emerging consensus that early integration of synthesis constraints yields more practical candidate molecules. Open questions remain around the trade-offs between computational cost, the fidelity of synthesizability proxies, and the diversity of generated chemical space.

Related Works in Same Category

The following **5 sibling papers** share the same taxonomy leaf node with the original paper:

1. Prompt-based 3d molecular diffusion models for structure-based drug design

Authors: L Yang, Z Huang, X Zhou, M Xu, W Zhang, et al. (6 authors total) | **Year/Venue**: 2023 | **URL**: View paper

Abstract

â¦ holds substantial promise for advancing structure-based drug design. Existing methods generate â¦ properties such as high binding affinity and synthesizability, to steer the diffusion model â¦

Relationship Analysis

Both papers belong to the category of structure-based generative models that optimize binding affinity alongside synthesizability and other drug-like properties. They overlap in addressing the challenge of generating 3D ligands with high binding affinity to protein targets using diffusion-based approaches. However, the original paper (SYNC) focuses on developing a synthesizability classifier as a plug-and-play module to guide existing SBDD methods through guided diffusion and DPO, while the candidate paper (PromptDiff) introduces a prompt-based diffusion framework that retrieves high-affinity ligand prompts to steer molecular generation, without explicitly addressing synthesizability evaluation as a core contribution.

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2. MedSAGE: Bridging Generative AI and Medicinal Chemistry for Structure-Based Design of Small Molecule Drugs

Authors: Alexander S. Powers, Tianyu Lu, Rohan V. Koodli, Minkai Xu, Siyi Gu, et al. (8 authors total) | **Year/Venue**: 2025 | **URL**: View paper

Abstract

Abstract While generative AI is transforming the de novo design of proteins, its effectiveness for structure-based design of small molecules remains limited. Current methods, including diffusion models, often produce small molecules with difficult-to-synthesize structures, poor medicinal chemistry properties, and limited target selectivity. To address these limitations, we introduce MedSAGE, a novel generative AI framework that adapts diffusion models specifically for de novo small-molecule desi...

Relationship Analysis

Both papers belong to the category of structure-based generative models that optimize binding affinity alongside synthesizability and other drug-like properties. They share the common goal of generating synthesizable 3D molecules for drug design, with SYNC focusing on developing a synthesizability classifier and classifier-driven generation paradigms (guided diffusion and DPO), while MedSAGE addresses synthesizability through a fragment-based representation in latent space with connectivity optimization. The key difference is that SYNC proposes a 3D-aware SE(3)-invariant classifier as a plug-and-play module to guide existing diffusion models, whereas MedSAGE develops a novel fragment-based generative framework with an interpretable latent space and connectivity algorithm.

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3. Synthesis-driven design of 3D molecules for structure-based drug discovery using geometric transformers

Authors: Li Yibo, Pei, Jianfeng, Yibo Li, Lai, et al. (8 authors total) | **Year/Venue**: 2022 | **URL**: View paper

Abstract

Finding drug-like compounds with high bioactivity is essential for drug discovery, but the task is complicated by the high cost of chemical synthesis and validation. With their outstanding performance in de novo drug design, deep generative models represent promising tools for tackling this challenge. In recently years, 3D molecule generative models have gained increasing attention due to their ability to directly utilize the 3D interaction information between the target and ligand. However, it ...

Relationship Analysis

Both papers belong to the category of structure-based generative models that optimize binding affinity alongside synthesizability and other drug-like properties. They overlap in addressing the synthesizability challenge in 3D molecule generation for SBDD, with both proposing methods to generate molecules with improved synthetic accessibility. The key difference is that the original paper (SYNC) focuses on developing a 3D-aware synthesizability classifier as a plug-and-play module for guiding existing diffusion-based SBDD methods, while the candidate paper (DeepLigBuilder+) proposes a reaction-based generation framework that directly incorporates synthetic pathways using purchasable building blocks and tree-based organization combined with SE(3)-equivariant transformers.

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4. Enhancing Ligand Validity and Affinity in Structure-Based Drug Design with Multi-Reward Optimization

Authors: S Lee, M Jo, J Ok, D Kim | **Year/Venue**: 2025 | **URL**: View paper

Abstract

â¦ ligand molecules that simultaneously optimize multiple objectives â such as binding affinity, synthetic accessibility, and strain energy â is a central challenge in structure-based â¦ feasibilityâ¦

Relationship Analysis

Both papers belong to the category of structure-based generative models that optimize binding affinity alongside synthesizability and other drug-like properties. They overlap in addressing the challenge of generating 3D ligands with multiple desirable properties beyond binding affinity, including synthesizability/validity and drug-likeness. The key difference is that the original paper (SYNC) focuses on developing a novel 3D-aware synthesizability classifier and integrating it through guided diffusion and DPO, while the candidate paper

proposes a multi-reward optimization framework using direct preference optimization for a Bayesian flow network to simultaneously optimize binding affinity, validity, and drug-likeness without introducing a new synthesizability metric.

5. FragGen: towards 3D geometry reliable fragment-based molecular generation

Authors: Odin Zhang, Yufei Huang, Shichen Cheng, Mengyao Yu, Xujun Zhang, et al. (19 authors total) | **Year/Venue**: 2024 • Chemical Science | **URL**: View paper

Abstract

3D structure-based molecular generation is a successful application of generative AI in drug discovery. Most earlier models follow an atom-wise paradigm, generating molecules with good docking scores but poor molecular properties (like synthesizability and drugability). In contrast, fragment-wise generation offers a promising alternative by assembling chemically viable fragments. However, the co-design of plausible chemical and geometrical structures is still challenging, as evidenced by existin...

Relationship Analysis

Both papers belong to the category of structure-based generative models that optimize binding affinity alongside synthesizability and other drug-like properties. They overlap in addressing the synthesizability challenge in 3D molecular generation for drug design, with both proposing methods to improve the chemical feasibility of generated molecules. However, SYNC focuses on developing a 3D-aware synthesizability classifier as a plug-and-play evaluation metric and guidance module for existing diffusion-based SBDD methods, while FragGen introduces a fragment-based generation approach using a Deep Geometry Handling protocol that decomposes geometry into multiple variable sets to ensure both geometric quality and synthesizability from the ground up.

Contributions Analysis

This paper presents **3 main contributions**, each analyzed against relevant prior work:

Contribution 1: Comprehensive benchmark of synthesizability metrics for SBDD

Description: The authors establish a new benchmark that evaluates eight classical synthesizability metrics across five curated datasets containing easy-to-synthesize and hard-to-synthesize molecules. This benchmark reveals significant inconsistencies between existing metrics and provides a comprehensive evaluation of 11 SBDD methods.

This contribution was assessed against **10 related papers** from the literature. Papers with potential prior art are analyzed in detail with textual evidence; others receive brief assessments.

1. Synthesizable by Design: A Retrosynthesis-Guided Framework for Molecular Analog Generation

URL: View paper

Brief Assessment

Synthesizable by Design[19] focuses on retrosynthesis-guided analog generation for existing molecules, not on benchmarking synthesizability metrics across SBDD methods. The paper evaluates analog generation performance rather than comparing synthesizability metrics themselves.

2. Generative flows on synthetic pathway for drug design

URL: View paper

Brief Assessment

Generative Flows Pathways[64] focuses on generating synthesizable molecules through synthetic pathways using reaction templates and building blocks, not on benchmarking synthesizability metrics. The paper evaluates synthesizability using existing tools like AiZynthFinder rather than establishing a benchmark comparing multiple synthesizability metrics across curated datasets.

3. The elephant in the lab: synthesizability in generative small-molecule design

URL: View paper

Brief Assessment

Elephant in Lab[3] is an opinion piece providing a comprehensive overview of synthesizability challenges in molecular generation. It does not present a benchmark comparing synthesizability metrics across curated datasets or evaluate SBDD methods, which are the core novel contributions of the original paper.

4. ChemistGA: a chemical synthesizable accessible molecular generation algorithm for real-world drug discovery

URL: View paper

Brief Assessment

ChemistGA[46] focuses on a genetic algorithm approach for molecular generation with synthetic accessibility considerations, but does not establish a benchmark comparing multiple synthesizability metrics across curated datasets as the original paper does.

5. Integrating synthetic accessibility with AI-based generative drug design

URL: View paper

Brief Assessment

Integrating Synthetic Accessibility[2] focuses on benchmarking synthesizability metrics for general molecular generation and drug design, not specifically for structure-based drug design (SBDD) methods. The candidate evaluates metrics on chembl-derived datasets, while the original benchmarks metrics across SBDD-specific methods and curated easy/hard-to-synthesize datasets.

6. The synthesizability of molecules proposed by generative models

URL: View paper

Brief Assessment

Synthesizability of Molecules[62] focuses on evaluating synthesizability metrics for general molecular generation models (not specifically SBDD methods) and does not establish benchmarks for structure-based drug design tasks. The candidate examines synthesizability across different molecular databases and generation algorithms but does not address the specific context of protein pocket binding or SBDD methods.

7. Generative AI for designing and validating easily synthesizable and structurally novel antibiotics

URL: View paper

Brief Assessment

Generative AI Antibiotics[65] focuses on generative model design for antibiotic discovery with synthesizability constraints, not on benchmarking synthesizability metrics across multiple datasets and SBDD methods as the original paper does.

8. Directly optimizing for synthesizability in generative molecular design using retrosynthesis models

URL: View paper

Brief Assessment

Optimizing for Synthesizability[63] focuses on directly optimizing molecular generation using retrosynthesis models in goal-directed generation, not on benchmarking synthesizability metrics across SBDD methods. The candidate addresses a different problem space (generative optimization) rather than metric evaluation.

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9. Deep generative molecular design reshapes drug discovery

URL: View paper

Brief Assessment

Deep Generative Design[61] discusses synthesizability as one property among many in molecular generation but does not establish benchmarks comparing multiple synthesizability metrics across curated datasets for SBDD methods.

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10. Generate what you can make: achieving in-house synthesizability with readily available resources in de novo drug design

URL: View paper

Brief Assessment

Generate What You Make[5] focuses on in-house synthesizability using limited building blocks for de novo drug design, not on benchmarking synthesizability metrics for structure-based drug design (SBDD) methods.

Contribution 2: SYNC: SE(3)-invariant synthesizability classifier

Description: The authors introduce SYNC, a 3D-aware and SE(3)-invariant classifier for predicting molecular synthesizability. SYNC demonstrates superior generalizability and speed compared to existing metrics and is designed to be fast, differentiable, 3D structure-aware, and SE(3)-invariant.

This contribution was assessed against **7 related papers** from the literature. Papers with potential prior art are analyzed in detail with textual evidence; others receive brief assessments.

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1. Latent 3d graph diffusion

URL: View paper

Brief Assessment

Latent 3D Graph[69] focuses on conditional generation with SE(3)-invariant attributes for molecular discovery, not on developing a synthesizability classifier. The candidate mentions synthesizability only as an evaluation metric, not as a core contribution.

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2. ResGen is a pocket-aware 3D molecular generation model based on parallel multiscale modelling

URL: View paper

Brief Assessment

ResGen[68] focuses on pocket-aware 3D molecular generation using multiscale modeling, not on developing SE(3)-invariant classifiers for predicting synthesizability. The candidate's emphasis is on generation rather than synthesizability assessment.

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3. FAST AND FLEXIBLE 3D MOLECULE DESIGN FRAMEWORK FOR NOVEL ORGANIC OPTOELECTRONIC MATERIALS

URL: View paper

Brief Assessment

Fast Flexible 3D[71] focuses on organic optoelectronic materials design using a virtual particle method with 3D pretraining, not on synthesizability classification for drug design. The SE(3)-invariant backbone serves molecular generation and property prediction, not synthesizability assessment.

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4. Geometric deep learning on molecular representations

URL: View paper

Brief Assessment

Geometric Deep Learning[66] focuses on general geometric deep learning principles and SE(3)-equivariant architectures for molecular property prediction (energies, forces, wavefunctions), not specifically on synthesizability classification. The candidate discusses SE(3)-equivariant message passing networks for quantum chemistry applications, which is a different domain from the original paper's synthesizability prediction task.

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5. SE3Lig: SE (3)-equivariant CNNs for the reconstruction of cofactors and ligands in protein structures

URL: View paper

Brief Assessment

SE3Lig[67] focuses on predicting cofactor and ligand densities in protein structures for structure completion, not on molecular synthesizability classification. The two works address fundamentally different problems in structure-based design.

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6. Synthesis-driven design of 3D molecules for structure-based drug discovery using geometric transformers

URL: View paper

Brief Assessment

Synthesis-Driven 3D Design[15] focuses on a reaction-based generation framework with tree-based organization of building blocks for synthesizability, not on developing an SE(3)-invariant classifier for predicting synthesizability. The candidate uses an SE(3)-equivariant transformer for structure-based design tasks combined with MCTS, which serves a different purpose than SYNC's classification objective.

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7. Generating Optimal Molecules with Synthesizability and 3D Equivariant Conformational Constraints

URL: View paper

Brief Assessment

Optimal Molecules Synthesizability[70] appears to be a technical report title page with minimal content. The provided context contains only copyright and publication information, lacking any technical details about SE(3)-invariant classifiers or synthesizability prediction methods that could challenge the novelty of SYNC.

Contribution 3: Synthesizability classifier-driven SBDD paradigm

Description: The authors propose a paradigm that integrates SYNC as a plug-and-play module into SBDD methods using two approaches: guided diffusion and Direct Preference Optimization (DPO). This paradigm enables generation of highly synthesizable molecules while preserving binding affinity without requiring additional binding constraints.

This contribution was assessed against **10 related papers** from the literature. Papers with potential prior art are analyzed in detail with textual evidence; others receive brief assessments.

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1. Equivariant diffusion for structure-based de novo ligand generation with latent-conditioning

URL: View paper

Brief Assessment

Equivariant Diffusion Ligand[55] focuses on latent-conditioned diffusion for hit expansion using reference molecules, not on integrating synthesizability classifiers into SBDD via guided diffusion or DPO.

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2. Graph diffusion transformers for multi-conditional molecular generation

URL: View paper

Brief Assessment

Graph Diffusion Transformers[57] focuses on multi-conditional molecular generation using diffusion models with property encoders, not on integrating synthesizability classifiers into SBDD methods through guided diffusion or DPO as proposed in the original paper.

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3. Diffusion Models for 3D Molecular and Crystal Structure Generation: Advancing Materials Discovery through Equivariance, Multi-Property Design, and Synthesizability

URL: View paper

Brief Assessment

Diffusion for Materials[53] is a review paper discussing general principles of integrating synthesizability into materials discovery. It does not present a specific paradigm combining SYNC with guided diffusion and DPO for SBDD.

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4. PILOT: equivariant diffusion for pocket-conditioned de novo ligand generation with multi-objective guidance via importance sampling

URL: View paper

Brief Assessment

PILOT[59] focuses on multi-objective guidance via importance sampling for property optimization during inference, not on integrating synthesizability classifiers as plug-and-play modules into SBDD methods using guided diffusion and DPO as training/fine-tuning paradigms.

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5. A chemically-guided generative diffusion model for materials synthesis planning

URL: View paper

Brief Assessment

Materials Synthesis Planning[56] focuses on zeolite synthesis planning using diffusion models for materials science, not structure-based drug design. The candidate addresses materials synthesis (zeolites, crystalline nanoporous materials) rather than molecular drug design for protein pockets, representing a fundamentally different application domain despite both using diffusion-based generative approaches.

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6. Target-aware 3D molecular generation based on guided equivariant diffusion

URL: View paper

Brief Assessment

Target-aware 3D Generation[51] focuses on bond diffusion and property guidance for molecular generation, not on integrating synthesizability classifiers into SBDD methods using guided diffusion or DPO.

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7. LigandDiff: de novo ligand design for 3D transition metal complexes with diffusion models

URL: View paper

Brief Assessment

LigandDiff Metal Complexes[58] focuses on de novo design of transition metal complexes and ligand generation, not on structure-based drug design or synthesizability-guided diffusion for protein-ligand binding. The domains and technical approaches are fundamentally different.

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8. The rise of generative AI frameworks in drug discovery

URL: View paper

Brief Assessment

Rise of Generative AI[54] discusses generative AI frameworks broadly in drug discovery but does not present a specific paradigm integrating synthesizability classifiers into SBDD methods through guided diffusion or DPO.

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9. LigandDiff: 3D Transition Metal Complex Generation with Diffusion Models

URL: View paper

Brief Assessment

LigandDiff 3D[60] focuses on generating transition metal complexes using diffusion models for organometallic compound design, not on integrating synthesizability classifiers into structure-based drug design or guided diffusion for protein-ligand binding.

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10. Decompopt: Controllable and decomposed diffusion models for structure-based molecular optimization

URL: View paper

Brief Assessment

Decompopt[52] focuses on molecular optimization through decomposed diffusion models for controllable generation tasks (r-group design, scaffold hopping), not on integrating synthesizability classifiers into SBDD via guided diffusion or DPO as a plug-and-play module.

Appendix: Text Similarity Detection

Textual similarity detection checked 31 papers and found 2 similarity segment(s) across 1 paper(s).

The following **1 paper(s)** were detected to have high textual similarity with the original paper. These may represent different versions of the same work, duplicate submissions, or papers with substantial textual overlap. Readers are advised to verify these relationships independently.

1. Prompt-based 3d molecular diffusion models for structure-based drug design

Detected in: Core Task (sibling)

⚠ **Note**: This paper shows substantial textual similarity with the original paper. It may be a different version, a duplicate submission, or contain significant overlapping content. Please review carefully to determine the nature of the relationship.

References

- [0] SYNC: Measuring and Advancing Synthesizability in Structure-Based Drug Design View paper
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